Process for the preparation of a solid, orally administrable pharmaceutical composition

The present invention relates to a process for the preparation of a solid, orally administrable pharmaceutical composition, comprising 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in hydrophilized form, and its use for the prophylaxis and/or treatment of diseases.

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (I) is a low molecular weight, orally administrable inhibitor of blood clotting factor Xa, which can be employed for the prophylaxis and/or treatment of various thromboembolic diseases (for this see WO-A 01/47919, whose disclosure is hereby included by way of reference). If, below, the discussion is of the active compound (I), all modifications of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (I), and the respective hydrates are additionally included.

The active compound (I) has a relatively poor water solubility (about 7 mg/l). As a result of this, difficulties with the oral bioavailability and an increased biological variability of the absorption rate can result.

To increase the oral bioavailability, various concepts have been described in the past:

Thus, solutions of active compounds are frequently used which can be filled, for example, into soft gelatine capsules. On account of the poor solubility of the active compound (I) in the solvents used for this purpose, this option is not applicable, however, in the present case, since, in the necessary dose strength, capsule sizes would result which are no longer swallowable.

An alternative process is the amorphization of the active compound. Here, the solution method proves problematical, since the active compound (I) is also poorly soluble in pharmaceutically acceptable solvents such as ethanol or acetone. Amorphization of the active compound by means of the fusion method is also disadvantageous because of the high melting point of the active compound (about 230°C), since an undesirably high proportion of breakdown components is formed during the preparation.

Furthermore, a process for the hydrophilization of hydrophobic active compounds as exemplified by hexobarbital and phenytoin has been described (Lerk, Lagas, Fell, Nauta, *Journal of Pharmaceutical Sciences* Vol. 67, No. 7, July 1978, 935 – 939: "Effect of Hydrophilization of Hydrophobic Drugs on Release Rate from Capsules"; Lerk, Lagas, Lie-A-Huen, Broersma, Zuurman, *Journal of Pharmaceutical Sciences* Vol. 68, No. 5, May 1979, 634-638: "In Vitro and In Vivo Availability of

Hydrophilized Phenytoin from Capsules"). The active compound particles are blended here in a mixer with a methyl- or hydroxyethylcellulose solution with extensive avoidance of an agglomeration step and then dried. The active compound thus obtained is subsequently filled into hard gelatine capsules without further treatment.

Surprisingly, it has now been found that a special treatment of the surface of the active compound (I) in the course of the moist granulation brings about improved absorption behaviour. The use of the active compound (I) in hydrophilized form in the preparation of solid, orally administrable pharmaceutical compositions leads to a significant increase in the bioavailability of the formulation thus obtained.

The present invention relates to a process for the preparation of a solid, orally administrable pharmaceutical composition comprising 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in hydrophilized form, in which

(a) first granules comprising the active compound (I) in hydrophilized form are prepared by moist granulation

(b) and the granules are then converted into the pharmaceutical composition, if appropriate with addition of pharmaceutically suitable additives.

The moist granulation in process step (a) can be carried out in a mixer (= mixer granulation) or in a fluidized bed (= fluidized bed granulation); fluidized bed granulation is preferred.

In the moist granulation, the active compound (I) can either be introduced into the pre-mixture (original mixture) as a solid or it is suspended in the granulating liquid. Preferably, the active compound (I) suspended in the granulating liquid is introduced into the moist granulation (suspension process).

In a preferred embodiment of the present invention, the active compound (I) is employed in crystalline form.

In a particularly preferred embodiment of the present invention, the crystalline active compound (I) is employed in micronized form. The active compound (I) in this case preferably has an average particle size X_{50} of less than 10 μm, in particular between 1 and 8 μm, and X_{90} (90% proportion) of less than 20 μm, in particular of less than 15 μm.

The granulating liquid used according to the invention contains a solvent, a hydrophilic binding agent and, if appropriate, a wetting agent. The hydrophilic binding agent is in this case dispersed in the granulating liquid or preferably dissolved therein.

The solvents used for the granulating liquid can be organic solvents, such as, for example, ethanol or acetone, or water or mixtures thereof. Preferably, water is used as a solvent.

The hydrophilic binding agents employed for the granulating liquid are pharmaceutically suitable hydrophilic additives, preferably those which dissolve in the solvent of the granulating liquid.

Preferably, hydrophilic polymers such as, for example, hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (sodium and calcium salts), ethylcellulose, methylcellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, hydroxypropylcellulose (HPC), L-HPC (low-substituted HPC), polyvinylpyrrolidone, polyvinyl alcohol, polymers of acrylic acid and its salts, vinylpyrrolidone-vinyl acetate copolymers (for example Kollidon® VA64, BASF), gelatine, guar gum, partially hydrolysed starch, alginates or xanthan are employed here. Particularly preferably, HPMC is employed as a hydrophilic binding agent.

The hydrophilic binding agent can be present here in a concentration of 1 to 15% (based on the total mass of the pharmaceutical composition), preferably of 1 to 8%.

The optionally present wetting agents employed for the granulating liquid are pharmaceutically suitable wetting agents (surfactants). The following may be mentioned, for example:

sodium salts of fatty alcohol sulphates such as sodium lauryl sulphate, sulphosuccinates such as sodium dioctyl sulphosuccinate, partial fatty acid esters of polyhydric alcohols such as glycerol monostearate, partial fatty acid esters of sorbitan such as sorbitan monolaurate, partial fatty acid esters of polyhydroxyethylenesorbitan such as polyethylene glycol sorbitan monolaurate, monostearate or monooleate, polyhydroxyethylene fatty alcohol ethers, polyhydroxyethylene fatty acid esters, ethylene oxide-propylene oxide block copolymers (Pluronic®) or ethoxylated triglycerides. Preferably, sodium lauryl sulphate is employed as a wetting agent.

If required, the wetting agent is employed in a concentration of 0.1 to 5% (based on the total mass of the pharmaceutical composition), preferably of 0.1 to 2%.

In the pre-mixture (original mixture) of the moist granulation, further pharmaceutically suitable additives are present. The following may be mentioned, for example:

- fillers and dry binding agents such as cellulose powder, microcrystalline cellulose, silicified microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, magnesium trisilicate, mannitol, maltitol, sorbitol, xylitol, lactose (anhydrous or as a hydrate, for example monohydrate), dextrose, maltose, sucrose, glucose, fructose or maltodextrins

- disintegration promoters (disintegrants) such as carboxymethylcellulose, croscarmellose (crosslinked carboxymethylcellulose), crospovidone (crosslinked polyvinylpyrrolidone), L-HPC (low-substituted hydroxypropylcellulose), sodium carboxymethyl starch, sodium glycolate of potato starch, partially hydrolysed starch, wheat starch, maize starch, rice starch or potato starch

In the case of tablet formulations having modified (delayed) release of active compound, instead of the disintegration promoter (disintegrant) substances can be present which influence the release rate. The following may be mentioned, for example: hydroxypropylcellulose, hydroxypropyl-methylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose, galactomannan, xanthan, glycerides, waxes, acrylic and/or methacrylic acid ester copolymers with trimethylammonium methylacrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic acid esters, polymers of methacrylic acid or methacrylic acid esters, ethyl acrylate-methyl methacrylate copolymers or methacrylic acid-methyl acrylate copolymers.

The granules obtained in process step (a) are subsequently converted into the pharmaceutical composition according to the invention in process step (b).

Process step (b) comprises, for example, tabletting, filling into capsules, preferably hard gelatine capsules, or filling as sachets, in each case according to customary methods familiar to the person skilled in the art, if appropriate with addition of further pharmaceutically suitable additives.

Pharmaceutically suitable additives which may be mentioned are, for example:

- lubricants, glidants, flow regulating agents such as fumaric acid, stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, higher molecular weight fatty alcohols, polyethylene glycols, starch (wheat, rice, maize or potato starch), talc, highly disperse (colloidal) silica, magnesium oxide, magnesium carbonate or calcium silicate

- disintegration promoters (disintegrants) such as carboxymethylcellulose, croscarmellose (crosslinked carboxymethylcellulose), crospovidone (crosslinked polyvinylpyrrolidone),

L-HPC (low-substituted hydroxypropylcellulose), sodium carboxymethyl starch, partially hydrolysed starch, wheat starch, maize starch, rice starch or potato starch

The present invention further relates to a solid, orally administrable pharmaceutical composition, comprising 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (I) in hydrophilized form.

The solid, orally administrable pharmaceutical composition according to the invention by way of example and preferably comprises granules, hard gelatine capsules or sachets filled with granules, and tablets releasing the active compound (I) rapidly or in a modified (delayed) manner. Tablets are preferred, in particular tablets rapidly releasing the active compound (I). In the context of the present invention, rapid-release tablets are in particular those which, according to the USP release method using apparatus 2 (paddle), such as described in the experimental section in chapter 5.2.2., have a Q value (30 minutes) of 75%.

The active compound (I) can be present in the pharmaceutical composition according to the invention in a concentration of 0.1 to 60%, preferably in a concentration of 1 to 40%, based on the total mass of the formulation. Here, the dose of the active compound (I) is preferably 1 to 100 mg.

If appropriate, the granules of tablets according to the invention are coated in a further step under customary conditions familiar to the person skilled in the art. The coating is carried out with addition of customary coating and film-forming agents familiar to the person skilled in the art, such as hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, polyvinyl-pyrrolidone, vinylpyrrolidone-vinyl acetate copolymers (for example Kollidon® VA64, BASF), shellac, acrylic and/or methacrylic acid ester copolymers with trimethylammonium methylacrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic acid esters, polymers of methacrylic acid or methacrylic acid esters, ethyl acrylate-methyl methacrylate copolymers, methacrylic acid-methyl acrylate copolymers, propylene glycol, polyethylene glycol, glycerol triacetate, triethyl citrate and/or colour additives/pigments such as, for example, titanium dioxide, iron oxide, indigotin or suitable colour lakes.

The present invention further relates to the use of the pharmaceutical composition according to the invention for the prophylaxis and/or treatment of diseases, in particular of thromboembolic diseases such as cardiac infarct, angina pectoris (including unstable angina), reocclusions and restenoses after

an angioplasty or aortocoronary bypass, cerebral infarct, transitory ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

The invention is illustrated in greater detail below by means of preferred exemplary embodiments, to which, however, it is not restricted. If not stated otherwise, all quantitative data below relate to percentages by weight.

Experimental section

1. Tablet preparation using granules comprising the active compound (I) in hydrophilized form/fluidized bed granulation process

1.1 Tablet composition (in mg/tablet)

Active compound (I), micronized	20.0 mg
Microcrystalline cellulose	35.0 mg
Lactose monohydrate	22.9 mg
Croscarmellose (Ac-Di-Sol®, FMC)	3.0 mg
Hydroxypropylmethylcellulose, 5 cp	3.0 mg
Sodium lauryl sulphate	0.5 mg
Magnesium stearate	0.6 mg
Hydroxypropylmethylcellulose, 15 cp	1.5 mg
Polyethylene glycol 3.350	0.5 mg
Titanium dioxide	0.5 mg
	87.5 mg

1.2 Preparation

Hydroxypropylmethylcellulose (5 cp) and sodium lauryl sulphate are dissolved in water. The micronized active compound (I) is suspended in this solution. The suspension thus prepared is sprayed onto the original mixture of microcrystalline cellulose, lactose monohydrate and croscarmellose as a granulating liquid in the course of a fluidized bed granulation. After drying and sieving (0.8 mm mesh width) the resulting granules, magnesium stearate is added and mixed. The press-ready mixture thus obtained is compressed to give tablets having a 6 mm diameter and a fracture resistance of 50 – 100 N. The subsequent coating of the tablets is carried out using titanium dioxide, which is suspended in an aqueous solution of hydroxypropylmethylcellulose (15 cp) and polyethylene glycol.

2. Tablet preparation using granules comprising the active compound (I) in hydrophilized form/high-speed granulation process

2.1 Tablet composition (in mg/tablet)

Active compound (I), micronized	5.0 mg
Microcrystalline cellulose	40.0 mg
Lactose monohydrate	33.9 mg
Croscarmellose (Ac-Di-Sol®, FMC)	3.0 mg
Hydroxypropylmethylcellulose, 3 cp	2.0 mg
Sodium lauryl sulphate	0.5 mg
Magnesium stearate	0.6 mg
Hydroxypropylmethylcellulose, 15 cp	1.5 mg
Polyethylene glycol 400	0.5 mg
Iron yellow	0.1 mg
Titanium dioxide	0.4 mg
	87.5 mg

2.2 Preparation

The substances cellulose, lactose monohydrate and croscarmellose employed are mixed in a high-speed mixer (original granule mixture). Hydroxypropylmethylcellulose (3 cp) and sodium lauryl sulphate are dissolved in water. The micronized active compound (I) is suspended in this solution. The suspension thus prepared is added to the original granule mixture as a granulating liquid and blended uniformly with the original granule mixture with the aid of the rapidly rotating stirrer. After thorough mixing has been carried out, the moist granules are sieved (4 mm mesh width) and dried in the fluidized bed. After sieving the dried granules (0.8 mm mesh width), magnesium stearate is added and mixed. The press-ready mixture thus obtained is compressed to give tablets having a 6 mm diameter and a fracture resistance of 50 – 100 N. The subsequent coating of the tablets is carried out using titanium dioxide and iron yellow, the pigments being suspended beforehand in an aqueous solution of hydroxypropylmethylcellulose (15 cp) and polyethylene glycol.

3. Preparation of granules comprising the active compound (I) in hydrophilized form and filling as sachets

3.1 Granule composition (in mg/sachet)

Active compound (I), micronized	50.0 mg
Mannitol	662.0 mg
Croscarmellose (Ac-Di-Sol®, FMC)	15.0 mg
Hydroxypropylmethylcellulose, 5 cp	15.0 mg
Sodium lauryl sulphate	1.0 mg
Highly disperse silica (Aerosil® 200, Degussa)	2.0 mg
Strawberry flavouring, spray-dried	5.0 mg
	750.0 mg

3.2 Preparation

Hydroxypropylmethylcellulose (5 cp) and sodium lauryl sulphate are dissolved in water. The micronized active compound (I) is suspended in this solution. The suspension thus prepared is sprayed onto the original mixture of mannitol and croscarmellose as a granulating liquid in the course of a fluidized bed granulation. After drying and sieving (0.8 mm mesh width) the resulting granules, highly disperse silica (Aerosil®) and strawberry flavouring are added and mixed. The mixture thus obtained is filled into sachet pouches to 750 mg with the aid of a sachet filling machine.

4. Preparation of granules comprising the active compound (I) in hydrophilized form and filling into hard gelatine capsules

4.1 Granule composition (in mg/capsule)

Active compound (I), micronized	20.0 mg
Microcrystalline cellulose	30.0 mg
Lactose monohydrate	79.5 mg
Maize starch	25.0 mg
Hydroxypropylmethylcellulose, 5 cp	4.5 mg
Sodium lauryl sulphate	0.5 mg
Highly disperse silica (Aerosil® 200, Degussa)	0.5 mg
	160.0 mg

4.2 Preparation

Hydroxypropylmethylcellulose (5 cp) and sodium lauryl sulphate are dissolved in water. The micronized active compound (I) is suspended in this solution. The suspension thus prepared is sprayed onto the original mixture of microcrystalline cellulose, lactose monohydrate and maize starch as a granulating liquid in the course of a fluidized bed granulation. After drying and sieving (0.8 mm mesh width) the resulting granules, highly disperse silica (Aerosil®) is added and mixed. The mixture obtained is filled to 160 mg in each case into hard gelatine capsules of capsule size 2.

5. Comparison of tablets with/without hydrophilized active compound (I)

5.1 Tablet composition, preparation

In order to investigate the tablet properties and the improved bioavailability of formulations containing hydrophilized active compound (I), uncoated tablets having a 10 mg active compound content (I) of the following composition are prepared (in mg/tablet):

Active compound (I), micronized	10.0 mg
Microcrystalline cellulose	40.0 mg
Lactose monohydrate	27.9 mg
Croscarmellose (Ac-Di-Sol®, FMC)	3.0 mg
Hydroxypropylmethylcellulose, 5 cp	3.0 mg
Sodium lauryl sulphate	0.5 mg
Magnesium stearate	0.6 mg
	85.0 mg

Tablet A: prepared by direct tabletting without granulation

Tablet B: prepared by the fluidized bed granulation/suspension process described in 1.2

The mixture for tablet A and the granules for tablet B are in each case pressed to give tablets having a diameter of 6 mm and a fracture strength of about 70 – 80 N.

5.2 Tablet properties

5.2.1 Disintegration time in water (USP disintegration tester, Erweka):

Tablet A: about 1.5 minutes

Tablet B: about 6.5 minutes

5.2.2 In-vitro release

The amounts of active compound released based on the declared total content of the tablets are shown in Table 1 below:

Table 1: In-vitro release

	15 min	30 min	45 min	60 min
Tablet A	87%	92%	93%	94%
Tablet B	94%	95%	96%	96%

(USP paddle, 900 ml of acetate buffer pH 4.5 + 0.5% sodium lauryl sulphate, 75 rpm)

5.2.3 Bioavailability

For the investigation of the bioavailability, three dogs were in each case administered three tablets of A or three tablets of B in cross-over fashion. The corresponding pharmacokinetic parameters after oral administration of 3 mg of active compound (I)/kg are listed in Table 2 below:

Table 2: Pharmacokinetic parameters of active compound (I)

		Animal			Mean	S.D.	Mean	S.D.
		1	2	3	geom.	geom.	arithm.	arithm.
Tablet A								
AUC(0-24)	[mg·h/l]	1.39	2.31	3.34	2.21	1.55	2.35	0.974
$AUC(0\text{-}24)_{norm}$	**[kg·h/l]**	**0.464**	**0.770**	**1.11**	**0.735**	**1.55**	**0.782**	**0.325**
C_{max}	[mg/l]	0.299	0.398	0.430	0.371	1.21	0.376	0.0684
$C_{max,norm}$	[kg/l]	0.0997	0.133	0.143	0.124	1.21	0.125	0.0228
$C(24)/C_{max}$	[%]	12.2	2.99	55.1	12.6	4.29	23.4	27.8
t_{max}	[h]	1.00	1.50	0.750	1.04	1.42	1.08	0.382
Tablet B								
AUC(0-24)	[mg·h/l]	2.82	3.03	3.73	3.17	1.16	3.19	0.476
$AUC(0\text{-}24)_{norm}$	**[kg·h/l]**	**0.938**	**1.01**	**1.24**	**1.06**	**1.16**	**1.06**	**0.159**
C_{max}	[mg/l]	0.478	0.513	0.321	0.428	1.29	0.437	0.102
$C_{max,norm}$	[kg/l]	0.159	0.171	0.107	0.143	1.29	0.146	0.0341
$C(24)/C_{max}$	[%]	26.4	1.17	93.4	14.2	9.53	40.3	47.7
t_{max}	[h]	1.00	1.50	0.750	1.04	1.42	1.08	0.382

Result: In spite of slower disintegration (see 5.2.1) and very similar in-vitro release (see 5.2.2) of tablet B in comparison to tablet A, tablet B has marked advantages in absorption and thus a bioavailability increased by about 35%. At the same time, a marked decrease in the variability is to be noted. The only difference between tablet A and tablet B is the hydrophilization of the active compound (I) in tablet B with the aid of the suspension process in the course of the moist granulation.